Solubility of 1,6,6-Trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-dione in Four Organic Solvents from (283.2 to 323.3) K

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The solubility of 1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-dione (tanshinone IIA) in ethanol, methanol, acetone, and ethyl acetate from (283.2 to 323.3) K was measured. The solubility of tanshinonone IIA in these solvents increases with increasing temperature. The solubility values were correlated with the Apelblat equation.

Introduction

1,6,6-Trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-dione (tanshinone IIA, $C_{19}H_{18}O_3$; molecular weight 294.33; CAS Registry Number 568-72-9; Figure 1) is an abietane-type diterpenoid isolated mainly from the roots and rhizome of *Salvia miltiorrhiza*, a traditionally used "blood invigorating" Chinese medicine.[1] It has been considered as the primary effective constituent and used as a quality controller of this species for many years.[2] Current pharmacological studies have demonstrated that tanshinone IIA possesses various activities such as neuroprotective effects,[3] anti-inflammation,[4] anticancer,[5] antioxidant, and cardiac myocytes protection,[6] etc. Moreover, a well-known Chinese drug sodium tanshinone IIA sulfonate (STS) which is clinically used to treat patients with cardiac metabolic disorders[7] is in fact a product derived from tanshinone IIA by structure modification. Nowadays, the main source for tanshinone IIA is from extraction from the plant *S. miltiorrhiza* followed by recrystallization from the solution, where organic solvents such as ethanol, methanol, acetone, or ethyl acetate are widely used.[8] Therefore, it is important to determine the solubility data of tanshinone IIA in different solvents.

In this study, the solubility of tanshinone IIA in four commonly used solvents, ethanol, methanol, acetone, and ethyl acetate, over the temperature range of (283.2 to 323.3) K was measured by HPLC, and the results were fitted with the modified Apelblat equation.

Experimental Section

Reagents and Apparatus. Tanshinone IIA was supplied by Guanyu Biology Technology Co. (Xi'an, China) with a minimum purity of 99.0 %. All organic solvents used were analytical purity grade and obtained from Shuanglin Chemical Reagent Factory (Hangzhou, China). Redistilled deionized water was used throughout. The solvent of the mobile phase was Burdick and Jackson ACS/HPLC Certified. A THZ-C shaker was supplied by Taicang Laboratorial Equipment Factory (Hangzhou, China), and a Waters 2996 HPLC instrument coupled with a 2487 UV detector was used for analysis of samples.

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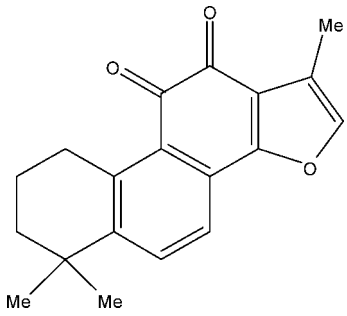

Figure 1. Chemical structure of tanshione IIA.

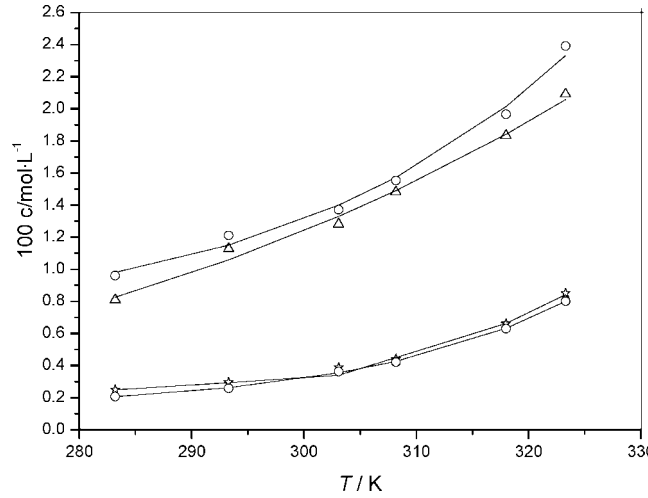

Figure 2. Experimental solubility of tanshinone IIA at different temperatures in four solvents: ○, acetone; Δ, ethyl acetate; ☆, ethanol; □, methanol. The corresponding lines are from the calculated values by eq 1.

Sample Preparation. Excess amounts of tanshinone IIA were added to 5 mL of four organic solvents (ethanol, methanol, acetone, and ethyl acetate) with their temperatures ranging from (283.2 to 323.3) K. The temperature was controlled by a thermostat (uncertainty of ± 0.1 K) in the shaker. The suspended solution was kept shaken for 24 h in the shaker. After attaining equilibrium, the supernatant liquid was withdrawn and filtered through a 0.45 μm membrane. The filtered samples were poured into a 50 mL volumetric

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Table 1. Mole Fraction Solubility c of Tanshinone IIA in Ethanol (1), Methanol (2), Acetone (3), and Ethyl Acetate (4)

T/K	c_1	$c_1-c_1^c$	c_2	$c_2-c_2^c$	c_3	$c_3-c_3^c$	c_4	$c_4-c_4^c$
				10^2 mol·L^{-1}				
283.2	0.249 ± 0.003	0.000	0.207 ± 0.002	−0.001	0.960 ± 0.003	0.021	0.809 ± 0.005	0.017
293.3	0.295 ± 0.003	−0.002	0.258 ± 0.002	0.004	1.211 ± 0.002	−0.061	1.128 ± 0.004	−0.070
303.1	0.389 ± 0.002	−0.049	0.363 ± 0.003	−0.008	1.372 ± 0.004	0.028	1.281 ± 0.004	0.049
308.2	0.441 ± 0.003	0.009	0.421 ± 0.004	0.005	1.553 ± 0.003	0.019	1.482 ± 0.008	0.008
318.0	0.661 ± 0.002	0.002	0.630 ± 0.002	0.002	1.965 ± 0.005	0.049	1.833 ± 0.005	0.008
323.3	0.852 ± 0.005	−0.010	0.801 ± 0.002	−0.001	2.392 ± 0.004	−0.060	2.091 ± 0.007	−0.034

flask and diluted to a fixed volume for HPLC analysis. Each measurement was repeated three times.

Sample Analysis. To determine the concentration of tanshinone IIA, an HPLC system mentioned above was used with its wavelength of detection set at 270 nm. All chromatographic separations were performed at 30 °C using a Phenomenex chromatography column (Gemini 5 μ, C_{18}, 110A, 250 × 4.60 mm, 5 micron). The mobile phase was methanol (1) + water (2) with a volume fraction of $\phi_1 = 0.85$ and its flow rate at 1.0 mL·min^{-1} and injection volume being 20 μL. The calibration curve for estimation of tanshinone IIA was established by using the standard solutions in the appropriate concentration range.

Result and Discussion

The solubility values of tanshinone IIA in ethanol, methanol, acetone, and ethyl acetate were measured with their data summarized in Table 1 where the values after +/− represent the uncertainties of the solubility. The solubility of tanshinone IIA in acetone is the highest, whereas that in methanol is the lowest. To the best of our knowledge, the polarity of the tested solvents is in the order: ethyl acetate < acetone < ethanol < methanol. It seemed that tanshinone IIA should be dissolved more easily in ethyl acetate than in acetone because it is a strong hydrophobic molecule with its dipole moment being 1.902.[9] However, our research work indicated that acetone displays better solvency than ethyl acetate for the title compound. It was hypothesized the structure similarity between the solvent and solute due to the ketone group enhanced significantly the solubility, corresponding to the empirical rule "like dissolves like" to some extent. Further studies are needed to explain this phenomenon.

The experimental solubility of tanshinone IIA increases with an increase in temperature (Figure 2). Thus, the solubility of tanshinone IIA as a function of temperature in pure solvents is correlated by the modified Apelblat equation.[10–14]

$$\ln(c/\text{mol}\cdot\text{L}^{-1}) = A + \frac{B}{T/\text{K}} + C\ln(T/\text{K}) \qquad (1)$$

where A, B, and C are the parameters; T is the absolute temperature; and c is the mole fraction solubility of tanshinone IIA. The experimental solubility values have been correlated with eq 2 by the least-squares method (see below). The regressed values of the parameters A, B, and C for the modified Apelblat equation are listed in Table 2 together with the root-mean-square deviation (rmsd), namely, standard deviation, which is defined as the following

$$\text{rmsd} = \sqrt{\frac{\sum_{i=1}^{N}(c_i^c - c_i)^2}{N}} \qquad (2)$$

where N is the number of experimental points and c_i and c_i^c denote the experimental and calculated values of the solubility, respectively. The calculated solubility of tanshinone IIA

Table 2. Parameters of Equation 1 for Tanshinone IIA in Solvents

solvent	A	B	C	10^4 rmsd
ethanol	−682.093	28110.265	102.165	2.08
methanol	−532.192	21087.975	79.974	6.56
acetone	−314.93	12311.78	47.259	4.34
ethyl acetate	−20.000	−1066.861	3.36	3.85

at different temperatures in four solvents (methanol, ethanol, ethyl acetate, and acetone) accords with the experimental data, which was also shown in Figure 2.

From Tables 1 and 2, it could be seen that the calculated solubilities showed good agreement with experimental values, indicating the modified Apelblat equation could be applied to correlate the solubility data of tanshinone IIA in the four organic solvents. The results show the solubility of tanshinone IIA in these solvents increases with an increase of temperature. As far as we know, heating might lower the intermolecular energy and thus accelerate the solute molecules diffusing to a solvent system. The experimental solubility and the modified Apelblat equation with the parameters might be used as essential data in purification and crystallization of tanshinone IIA.

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Supporting Information Available:

The experimental values of tanshinone IIA in four solvents, acetone, ethyl acetate, ethanol, and methanol, from (283.2 to 323.3) K (Tables and Figure). This material is available free of charge via the Internet at http://pubs.acs.org.

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